

HCV INHIBITING SULFONAMIDES

- The present invention relates to the use of sulfonamides as inhibitors of HCV as well as their use in pharmaceutical compositions aimed to treat or combat HCV infections. The present invention also relates to the use of said sulfonamides in pharmaceutical compositions aimed to treat or combat combined HCV and HIV infections. In addition, the present invention relates to processes for preparation of such pharmaceutical compositions. The present invention also concerns combinations of the present sulfonamides with other anti-HCV agents and/or anti-HIV agents.
- Following its discovery in 1989 as the agent implicated in the majority of viral non-A, non-B hepatitis (Choo et al., *Science* 244, 359-362, 1989), hepatitis C virus (HCV) has become a focus of considerable medical research (Lauer, G.M and Walker, B.D., *New Eng. J Med.* 345, 41-52, 2001). HCV is a member of the *Flaviviridae* family of viruses in the *hepacivirus* genus, and is closely related to the *flavivirus* genus, which includes a number of viruses implicated in human disease, such as dengue virus and yellow fever virus, and to the animal *pestivirus* family, which includes bovine viral diarrhea virus (BVDV). HCV is a positive-sense, single-stranded RNA virus, with a genome of around 9,600 bp. The genome comprises both 5' and 3' untranslated regions which adopt RNA secondary structures, and a central open reading frame that encodes a single polyprotein of around 3,010-3,030 amino acids. The polyprotein encodes ten gene products which are generated from the precursor polyprotein by an orchestrated series of co- and posttranslational endoproteolytic cleavages mediated by both host and viral proteases. The viral structural proteins include the core nucleocapsid protein, and two envelope glycoproteins E1 and E2. The non-structural (NS) proteins encode some essential viral enzymatic functions (helicase, polymerase, protease), as well as proteins of unknown function. Replication of the viral genome is mediated by an RNA-dependent RNA polymerase, encoded by non-structural protein 5b (NS5B). In addition to the polymerase, the viral helicase and protease functions, both encoded in the bifunctional NS3 protein, have been shown to be essential for replication of HCV RNA in chimpanzee models of infection (Kolykhalov, A.A., Mihalik, K., Feinstone, S.M., and Rice, C.M. *J Virol.* 74, 2046-2051, 2000). In addition to the NS3 serine protease, HCV also encodes a metalloproteinase in the NS2 region.
- HCV replicates preferentially in hepatocytes but is not directly cytopathic, leading to persistent infection. In particular, the lack of a vigorous T-lymphocyte response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection. There are 6 major HCV genotypes and more than 50 subtypes, which are

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- differently distributed geographically. HCV type 1 is the predominant genotype in the US and Europe. For instance, HCV type 1 accounts for 70 to 75 percent of all HCV infections in the United States. The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining difficulties in vaccine development and the lack of response to therapy. An estimated 170 million persons worldwide are infected with hepatitis C virus (HCV). Following the initial acute infection, a majority of infected individuals develop chronic hepatitis, which can progress to liver fibrosis leading to cirrhosis, end-stage liver disease, and HCC (hepatocellular carcinoma) (National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C. *Hepatology*, 36, 5 Suppl. S3-S20, 2002). Liver cirrhosis due to HCV infection is responsible for about 10,000 deaths per year in the U.S.A. alone, and is the leading cause for liver transplantations. Transmission of HCV can occur through contact with contaminated blood or blood products, for example following blood transfusion or intravenous drug use. The introduction of diagnostic tests used in blood screening has led to a downward trend in post-transfusion HCV incidence. However, given the slow progression to the end-stage liver disease, the existing infections will continue to present a serious medical and economic burden for decades (Kim, W.R. *Hepatology*, 36, 5 Suppl. S30-S34, 2002).
- The treatment of this chronic disease is an unmet clinical need, since current therapy is only partially effective and limited by undesirable side effects.

- Current HCV therapies are based on (pegylated) interferon-alpha (IFN- $\alpha$ ) in combination with ribavirin. This combination therapy yields a sustained virologic response in more than 40% of patients infected by genotype 1 viruses and about 80% of those infected by genotypes 2 and 3. Beside the limited efficacy on HCV type 1, combination therapy has significant side effects and is poorly tolerated in many patients. For instance, in registration trials of pegylated interferon and ribavirin, significant side effects resulted in discontinuation of treatment in approximately 10 to 14 percent of patients. Major side effects of combination therapy include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. The development of more effective, convenient and tolerated treatments is a major public health objective.

- Thus, there is a high medical need for low molecular weight HCV inhibitors.

Furthermore, it is known that a large percentage of patients infected with human immunodeficiency virus 1 (HIV) are also infected with HCV, i.e. they are HCV/HIV co-infected. For instance, in the United States, about 25% of persons infected with HIV

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- are also infected with HCV (Sherman et al. 2002 Clin.Infect. Dis. 34:831-837). Given the differences in tissue and cell tropism for HIV and HCV, it seems likely that the impact of HIV on HCV liver disease results from damage to the immune system, rather than from direct effects of HIV enzymes on the HCV replication machinery. The effects of HCV infection on the course of HIV/AIDS are less well defined, and have focused primarily on the impact of liver disease on the tolerability of HAART (highly active antiretroviral therapy). HIV infection appears to adversely affect all stages of HCV infection, leading to increased viral persistence and accelerated progression of HCV-related liver disease. In turn, HCV infection may affect the management of HIV infection, increasing the incidence of liver toxicity caused by antiviral medications. The medical management of HCV in HIV-infected persons remains controversial due to the complexity of both infections, potential drug interactions, and the absence of information (Thomas, D. L. *Hepatology* 36, 5 Suppl:S201-S209, 2002).
- Thus, there is also a high medical need for low molecular weight HCV inhibitors, which may be efficacious in the treatment of HCV in HIV/HCV coinfecting patients.

- Although HCV/HIV coinfection is common, HCV and HIV belong to two completely different viral orders with different life cycles and host cell requirements. HCV is a flavivirus with a cytoplasmic replication cycle and tropism for the liver, although replication has also been detected in non-liver cells. Flaviviruses have no DNA steps in their life cycle. Although the development of an infectious HCV replication system has proven elusive, it is assumed that HCV may use specific cellular receptors to mediate its predominantly liver-specific replication. Human immunodeficiency viruses type 1 (HIV-1) and type 2 (HIV-2) are human lentiviruses belonging to the Retroviridae family. HIV infects T lymphocytes (particularly CD4 cells) and macrophages. Like other retroviruses HIV exhibits an integration step leading to insertion of the viral DNA sequence into the host DNA. The targeting of CD4+ cells by HIV results from HIV binding to the CD4 cell surface receptor. Further T cell tropism is determined by the utilization of two cellular co-receptors, termed the CC chemokine receptor 5 (CCR5) and the CXCR4 receptor 4 (CXCR4).

- Although some of the structures of the present invention have been described in WO 02/083657, WO 02/092595, WO 02/081478, WO 03/53435, PCT/EP03/50057, PCT/EP03/50173 and PCT/EP03/50359 as HIV protease inhibitors, they are not specifically disclosed, suggested or claimed therein in conjunction with HCV infection.

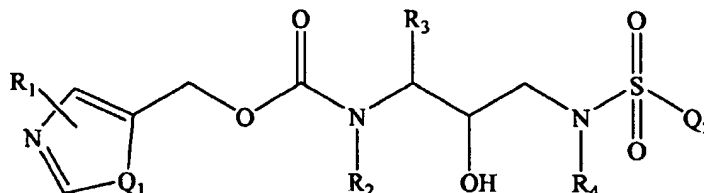
It is therefore surprising that the present sulfonamides are now found to have inhibitory activity against replication of HCV and can therefore be used in pharmaceutical

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compositions aimed to treat HCV infected patients, even to treat HCV infected patients co-infected with HIV.

### Detailed description

The present invention concerns the use of sulfonamide derivatives having the general formula



and *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs and esters thereof, wherein

$Q_1$  is -S- or -O-;

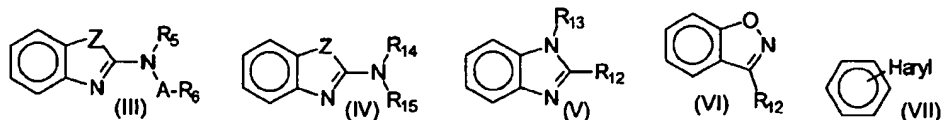
$R_1$  is hydrogen,  $C_{1-6}$ alkyl, hydroxy, amino, halogen, amino $C_{1-4}$ alkyl and mono- or di( $C_{1-4}$ alkyl)amino;

$R_2$ ,  $R_{14}$  and  $R_{15}$  are, each independently, hydrogen or  $C_{1-6}$ alkyl;

$R_3$  is  $C_{1-6}$ alkyl, aryl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl, or aryl $C_{1-4}$ alkyl;

$R_4$  is hydrogen,  $C_{1-4}$ alkyloxycarbonyl, carboxyl, optionally mono- or disubstituted aminocarbonyl, mono- or di( $C_{1-4}$ alkyl)aminocarbonyl,  $C_{3-7}$ cycloalkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl or  $C_{1-6}$ alkyl optionally substituted with one or more substituents each independently selected from aryl, Het<sup>1</sup>, Het<sup>2</sup>,  $C_{3-7}$ cycloalkyl,  $C_{1-4}$ alkyloxy-carbonyl, carboxyl, aminocarbonyl, mono- or di( $C_{1-4}$ alkyl)aminocarbonyl, aminosulfonyl,  $C_{1-4}$ alkylS(=O)<sub>2</sub>, hydroxy, cyano, halogen or amino optionally mono- or di-substituted where the substituents are each independently selected from  $C_{1-4}$ alkyl, aryl, aryl $C_{1-4}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl, Het<sup>1</sup>, Het<sup>2</sup>, Het<sup>1</sup> $C_{1-4}$ alkyl and Het<sup>2</sup> $C_{1-4}$ alkyl;

$Q_2$  is a radical of formula (III), (IV), (V), (VI), or (VII)



and is be attached to the remainder of the molecule via any available carbon atom of the phenyl or fused phenyl ring,

Z is O or S;

A is  $C_{1-6}$ alkanediyl, -C(=O)-, -C(=S)-, -S(=O)<sub>2</sub>-,  $C_{1-6}$ alkanediyl-C(=O)-,  $C_{1-6}$ alkanediyl-C(=S)- or  $C_{1-6}$ alkanediyl-S(=O)<sub>2</sub>-; wherein the point of attachment to the nitrogen atom is the  $C_{1-6}$ alkanediyl group in those moieties containing said group;

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- R<sub>5</sub> is hydrogen, hydroxy, C<sub>1-6</sub>alkyl, Het<sup>1</sup>C<sub>1-6</sub>alkyl, Het<sup>2</sup>C<sub>1-6</sub>alkyl, or aminoC<sub>1-6</sub>alkyl wherein the amino group may optionally be mono- or di-substituted with C<sub>1-4</sub>alkyl;
- 5 R<sub>6</sub> is C<sub>1-6</sub>alkyloxy, Het<sup>1</sup>, Het<sup>1</sup>oxy, Het<sup>2</sup>, Het<sup>2</sup>oxy, aryl, aryloxy or amino; and in case -A- is other than C<sub>1-6</sub>alkanediyl then R<sub>6</sub> may also be C<sub>1-6</sub>alkyl, Het<sup>1</sup>C<sub>1-4</sub>alkyl, Het<sup>1</sup>oxyC<sub>1-4</sub>alkyl, Het<sup>2</sup>C<sub>1-4</sub>alkyl, Het<sup>2</sup>oxyC<sub>1-4</sub>alkyl, arylC<sub>1-4</sub>alkyl, aryloxyC<sub>1-4</sub>alkyl or aminoC<sub>1-4</sub>alkyl; wherein each of the amino groups in the definition of R<sub>6</sub> may optionally be substituted with one or more substituents selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het<sup>1</sup>, Het<sup>2</sup>, arylC<sub>1-4</sub>alkyl, Het<sup>1</sup>C<sub>1-4</sub>alkyl or Het<sup>2</sup>C<sub>1-4</sub>alkyl;; and
- 10 R<sub>5</sub> and -A-R<sub>6</sub> taken together with the nitrogen atom to which they are attached may also form Het<sup>1</sup> or Het<sup>2</sup>;
- R<sub>12</sub> is hydrogen, -NH<sub>2</sub>, -N(R<sub>5</sub>)(AR<sub>6</sub>), -C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl-W-R<sub>17</sub>, wherein each C<sub>1-6</sub>alkyl may optionally be substituted with halogen, hydroxy, aryl, Het<sup>1</sup>, Het<sup>2</sup>, amino or mono- or di-(C<sub>1-4</sub> alkyl)amino;
- 15 W is oxy, carbonyl, oxycarbonyl, carbonyloxy, oxycarbonyloxy, amino, amino-carbonyl, carbonylamino or sulphur;
- R<sub>13</sub> is hydrogen or C<sub>1-6</sub>-alkyl optionally substituted with a substituent selected from the group consisting of aryl, Het<sup>1</sup>, Het<sup>2</sup>, hydroxy, halogen or amino, wherein the amino group may be optionally be mono- or di-substituted with C<sub>1-4</sub>alkyl;
- 20 R<sub>17</sub> is C<sub>1-6</sub>alkyl, aryl, Het<sup>1</sup> or Het<sup>2</sup>;
- Haryl is an aromatic monocyclic, bicyclic or tricyclic heterocycle having 3 to 14 ring members which contains one or more heteroatom ring members selected from nitrogen, oxygen and sulfur and which may optionally be substituted on (i) one or
- 25 more carbon atoms by a substituent selected from the group consisting of C<sub>1-6</sub>alkyl, halogen, hydroxy, optionally mono- or di-substituted amino, nitro, cyano, haloC<sub>1-6</sub>alkyl, carboxyl, C<sub>3-7</sub>cycloalkyl, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, aryl, -(R<sub>7a</sub>)<sub>n</sub>-M-R<sub>7b</sub>, Het<sup>1</sup> and Het<sup>2</sup>; wherein the optional substituents on any amino function in the above group of
- 30 substituents are independently selected from R<sub>5</sub> and -A-R<sub>6</sub>; and on (ii) a nitrogen atom if present by hydroxy or -A-R<sub>6</sub>;
- R<sub>7a</sub> is C<sub>1-6</sub>alkanediyl optionally substituted with one or more substituents selected from, halogen, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het<sup>1</sup> or Het<sup>2</sup>;
- 35 R<sub>7b</sub> is C<sub>1-6</sub>alkyl optionally substituted with one or more substituents selected from halogen, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het<sup>1</sup> or Het<sup>2</sup>;

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$R_8$  is hydrogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl, aryl $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-6}$ alkyl, aryl, Het<sup>1</sup>, Het<sup>1</sup> $C_{1-6}$ alkyl, Het<sup>2</sup> or Het<sup>2</sup> $C_{1-6}$ alkyl;  
 M is defined by -C(=O)-, -O-C(=O)-, -C(=O)-O-, -CH<sub>2</sub>-CHOH-, -CHOH-CH<sub>2</sub>-,  
 -NR<sub>8</sub>-C(=O)-, -(C=O)-NR<sub>8</sub>-, -S(=O)<sub>2</sub>-, -O-, -S-, -O-S(=O)<sub>2</sub>-, -S(=O)<sub>2</sub>-O-, -NR<sub>8</sub>-  
 5 S(=O)<sub>2</sub> or -S(=O)<sub>2</sub>-NR<sub>8</sub>-,  
 n is zero or 1;  
 for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV.

10 The further embodiments will become apparent throughout the description. It will be appreciated that the compounds described herein are intended for the use according to the invention.

This invention also envisions the quaternization of the nitrogen atoms of the present  
 15 compounds. A basic nitrogen can be quaternized with any agent known to those of ordinary skill in the art including, for instance, lower alkyl halides, dialkyl sulfates, long chain halides and aralkyl halides.

Whenever the term "substituted" is used in defining the compounds of formula (I), it is  
 20 meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a  
 25 therapeutic agent.

As used herein, the term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo or iodo.

30 The term " $C_{1-4}$ alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms, such as, for example, methyl, ethyl, propyl, butyl and 2-methyl-propyl, and the like.

The term " $C_{1-6}$ alkyl" as a group or part of a group defines straight and branched  
 35 chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for  $C_{1-4}$ alkyl and pentyl, hexyl, 2-methylbutyl, 3-methylpentyl and the like.

The term " $C_{1-6}$ alkanediyl" as a group or part of a group defines bivalent straight and

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branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, pentan-1,5-diyl, hexan-1,6-diyl, 2-methylbutan-1,4-diyl, 3-methylpentan-1,5-diyl and the like.

5

The term "C<sub>2-6</sub>alkenyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having from 2 to 6 carbon atoms containing at least one double bond such as, for example, ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like.

10

The term "C<sub>2-6</sub>alkynyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having from 2 to 6 carbon atoms containing at least one triple bond such as, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

15

The term "C<sub>3-7</sub>cycloalkyl" as a group or part of a group is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "aryl" as a group or part of a group is meant to include phenyl and naphthyl, which both may be optionally substituted with one or more substituents independently selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloC<sub>1-6</sub>alkyl, carboxyl, C<sub>1-6</sub>alkoxycarbonyl, C<sub>3-7</sub>cycloalkyl, Het<sup>1</sup>, optionally mono- or disubstituted aminocarbonyl, optionally mono- or disubstituted aminoC<sub>1-6</sub>alkyl, methylthio, methylsulfonyl, and phenyl optionally substituted with one or more substituents selected from the group consisting of C<sub>1-6</sub>alkyl, halogen, C<sub>1-6</sub>alkyloxy, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, carboxyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxycarbonyl, C<sub>3-7</sub>cycloalkyl, Het<sup>1</sup>, optionally mono- or di-substituted aminocarbonyl, methylthio and methylsulfonyl; wherein the optional substituents on any amino function of the above two groups of substituents are independently selected from the group consisting of C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy-A-, Het<sup>1</sup>-A-, Het<sup>1</sup>C<sub>1-6</sub>alkyl, Het<sup>1</sup>C<sub>1-6</sub>alkyl-A-, Het<sup>1</sup>oxy-A-, Het<sup>1</sup>oxyC<sub>1-6</sub>alkyl-A-, phenyl-A-, phenyl-oxy-A-, phenyloxyC<sub>1-6</sub>alkyl-A-, phenyl-, C<sub>1-6</sub>alkyl-A-, C<sub>1-6</sub>alkyloxycarbonylamino-A-, amino-A-, aminoC<sub>1-6</sub>alkyl and amino-C<sub>1-6</sub>alkyl-A-, wherein A is as defined above and wherein each of the amino groups in the latter group of substituents may optionally be mono- or, where possible, di-substituted with C<sub>1-6</sub>alkyl.

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The term "haloC<sub>1-6</sub>alkyl" as a group or part of a group is defined as C<sub>1-6</sub>alkyl substituted with one or more halogen atoms, preferably, chloro or fluoro atoms, more

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preferably fluoro atoms. Preferred haloC<sub>1-6</sub>alkyl groups include for instance trifluoromethyl and difluoromethyl.

- The term "Het<sup>1</sup>" as a group or part of a group is defined as a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 14 ring members, more preferably 5 to 10 ring members and more preferably 5 to 8 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms by a substituent selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, halogen, hydroxy, oxo, optionally mono- or disubstituted amino, nitro, cyano, haloC<sub>1-6</sub>alkyl, carboxyl, C<sub>1-6</sub>alkoxycarbonyl, C<sub>3-7</sub>cycloalkyl, optionally mono- or disubstituted aminocarbonyl, optionally mono- or disubstituted aminoC<sub>1-6</sub>alkyl, methylthio, methylsulfonyl, phenyl and a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having 3 to 14 ring members which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur; and wherein the optional substituents on any amino function in the above mentioned group of substituents are independently selected from the group of substituents consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxy-A-, Het<sup>2</sup>-A-, Het<sup>2</sup>C<sub>1-6</sub>alkyl, Het<sup>2</sup>C<sub>1-6</sub>alkyl-A-, Het<sup>2</sup>oxy-A-, Het<sup>2</sup>oxyC<sub>1-6</sub>alkyl-A-, phenyl-A-, phenyloxy-A-, phenyloxyC<sub>1-6</sub>alkyl-A-, phenylC<sub>1-6</sub>alkyl-A-, C<sub>1-6</sub>alkyloxycarbonylamino-A-, amino-A-, aminoC<sub>1-6</sub>alkyl and aminoC<sub>1-6</sub>alkyl-A-; wherein A is as defined above and wherein each of the amino groups in the latter group of substituents may optionally be mono- or where possible disubstituted with C<sub>1-6</sub>alkyl.
- The term "Het<sup>2</sup>" as a group or part of a group is defined as an aromatic monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 14 ring members, more preferably 5 to 10 ring members and more preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms by a substituent selected from the group of substituents consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloC<sub>1-6</sub>alkyl, carboxyl, C<sub>1-6</sub>alkoxycarbonyl, C<sub>3-7</sub>cycloalkyl, optionally mono- or disubstituted aminocarbonyl, optionally mono- or disubstituted aminoC<sub>1-6</sub>alkyl, methylthio, methylsulfonyl, aryl, and an saturated, partially saturated and aromatic monocyclic, bicyclic or tricyclic heterocycle having 3 to 14 ring members; wherein the optional substituents on any amino function in the above group of substituents are independently selected from the group of substituents consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxy-A-, C<sub>1-6</sub>alkyl-A-, aryl-A-, aryloxy-A-, aryloxyC<sub>1-6</sub>alkyl-A-, arylC<sub>1-6</sub>alkyl-A-, C<sub>1-6</sub>alkyloxy-



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carbonylamino-A-, amino-A-, aminoC<sub>1-6</sub>alkyl and aminoC<sub>1-6</sub>alkyl-A-; wherein A is as defined above and wherein each of the amino groups in the latter group of substituents may optionally be mono- or where possible di-substituted with C<sub>1-4</sub>alkyl.

- 5 As used herein, the term (=O) forms a carbonyl moiety with the carbon atom to which it is attached.

As used herein before, the term "one or more" covers the possibility of all the available C-atoms, where appropriate, to be substituted, preferably, one, two or three. Similarly,  
10 the term "one or more" covers the possibility of all the available N-atoms, where applicable, to be substituted, preferably, one or two.

When any variable (e.g. halogen or C<sub>1-4</sub>alkyl) occurs more than one time in any constituent, each definition is independent.  
15

The term "prodrug" as used throughout this text means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8<sup>th</sup> ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p 13-15) describing prodrugs generally is hereby incorporated. Prodrugs of  
20 a compound of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds  
25 of the present invention wherein a hydroxy group, for instance the hydroxy group on the asymmetric carbon atom, or an amino group is bonded to any group that, when the prodrug is administered to a patient, cleaves to form a free hydroxyl or free amino, respectively.

- 30 Typical examples of prodrugs are described for instance in WO 99/33795, WO 99/33815, WO 99/33793 and WO 99/33792, all incorporated herein by reference.

Prodrugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*.  
35

For therapeutic use, the salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically or physiologically acceptable. However, salts having a pharmaceutically unacceptable counterion may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound of formula (I).

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All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

5 The pharmaceutically acceptable or physiologically tolerable addition salt forms which the compounds of the present invention are able to form can conveniently be prepared using the appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methane-  
10 sulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids.

Conversely said acid addition salt forms can be converted by treatment with an appropriate base into the free base form.

15 The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt form by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for instance, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine,  
20 N-methyl, -D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said base addition salt forms can be converted by treatment with an appropriate acid into the free acid form.

25 The term "salts" also comprises the hydrates and the solvent addition forms which the compounds of the present invention are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

30 The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

The present compounds may also exist in their tautomeric forms. Such forms, although  
35 not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

The term stereochemically isomeric forms of compounds of the present invention, as used hereinbefore, defines all possible compounds made up of the same atoms bonded

by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the present invention may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said  
5 compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

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Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a  
15 stereoisomeric excess of at least 80% (i. e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a  
20 stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

25

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically  
30 isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

35

The diastereomeric racemates of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods which may advantageously be

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employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

It is clear to a person skilled in the art that the compounds of formula (I) contain at least one asymmetric center and thus may exist as different stereoisomeric forms. The absolute configuration of each asymmetric center that may be present in the compounds of formula (I) may be indicated by the stereochemical descriptors R and S, this R and S notation corresponding to the rules described in Pure Appl. Chem. 1976, 45, 11-30. The carbon atom marked with the asterisk (\*) preferably has the R configuration.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

Whenever used hereinafter, the term "compounds of formula (I)", or "the present compounds" or similar term is meant to include the compounds of general formula (I), their *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs and esters, as well as their quaternized nitrogen analogues.

A particular group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply :

- R<sub>1</sub> is hydrogen or halogen;
- R<sub>2</sub> is hydrogen;
- R<sub>3</sub> is arylC<sub>1-4</sub>alkyl;
- R<sub>4</sub> C<sub>1-6</sub>alkyl;
- Q<sub>2</sub> is a radical of formula (III) wherein Z is O;
- Q<sub>2</sub> is a radical of formula (III) wherein Z is S;
- Q<sub>2</sub> is a radical of formula (IV) wherein Z is O;
- Q<sub>2</sub> is a radical of formula (IV) wherein Z is S;
- Q<sub>2</sub> is a radical of formula (V);
- Q<sub>2</sub> is a radical of formula (VI);
- Q<sub>2</sub> is a radical of formula (VII);
- R<sub>5</sub> is hydrogen or C<sub>1-6</sub>alkyl; or taken together with -A-R<sub>6</sub> and with the nitrogen atom to which it is attached forms a Het<sup>1</sup>;
- A is C<sub>1-6</sub>alkanediyl or -C(=O)-;
- R<sub>6</sub> is C<sub>1-6</sub>alkyloxy, Het<sup>1</sup>, Het<sup>2</sup>, aryl or amino; and in case -A- is other than C<sub>1-6</sub>alkanediyl then R<sub>6</sub> may also be C<sub>1-6</sub>alkyl, Het<sup>1</sup>C<sub>1-4</sub>alkyl, Het<sup>2</sup>C<sub>1-4</sub>alkyl, arylC<sub>1-4</sub>alkyl or aminoC<sub>1-4</sub>alkyl; wherein each of the amino groups in the definition

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of R<sub>6</sub> may optionally be substituted with one or more substituents selected from C<sub>1-4</sub>alkyl, arylC<sub>1-4</sub>alkyl, Het<sup>1</sup>C<sub>1-4</sub>alkyl or Het<sup>2</sup>C<sub>1-4</sub>alkyl;

R<sub>12</sub> is hydrogen;

R<sub>13</sub> is hydrogen or C<sub>1-6</sub>-alkyl optionally substituted with aryl;

5 Haryl is thiazolyl or oxazolyl which may both optionally be substituted with C<sub>1-6</sub>alkyl or Het<sup>2</sup>amino;

A special group of compounds are those compounds of formula (I) wherein R<sub>2</sub> is hydrogen.

10

Another featured group of compounds are those compounds of formula (I), wherein R<sub>3</sub> is arylC<sub>1-4</sub>alkyl and R<sub>2</sub> is hydrogen.

Another featured group of compounds are those compounds of formula (I), wherein R<sub>4</sub> is C<sub>1-6</sub>alkyl, and in particular wherein R<sub>4</sub> is C<sub>1-6</sub>alkyl, R<sub>2</sub> is hydrogen, R<sub>3</sub> is arylC<sub>1-4</sub>alkyl.

15

Another featured group of compounds are those compounds of formula (I), as defined herein wherein R<sub>4</sub> is tert-butyl, butyl or isobutyl.

20

Another featured group of compounds are those compounds of formula (I), as defined herein, wherein Q<sub>2</sub> is a radical of formula (III), and in particular, those compounds of formula (I), as defined herein, wherein Q<sub>2</sub> is a radical of formula (III), R<sub>4</sub> is C<sub>1-6</sub>alkyl, R<sub>2</sub> is hydrogen, R<sub>3</sub> is arylC<sub>1-4</sub>alkyl.

25

Another featured group of compounds are those compounds of formula (I) as defined herein, wherein Q<sub>2</sub> is a radical of formula (IV), and in particular those compounds of formula (I), as defined herein, wherein Q<sub>2</sub> is a radical of formula (IV), R<sub>4</sub> is C<sub>1-6</sub>alkyl, R<sub>2</sub> is hydrogen, R<sub>3</sub> is arylC<sub>1-4</sub>alkyl.

30

Another featured group of compounds are those compounds of formula (I) as defined herein, wherein Q<sub>2</sub> is a radical of formula (V), and in particular those compounds of formula (I), as defined herein, wherein Q<sub>2</sub> is a radical of formula (V), R<sub>4</sub> is C<sub>1-6</sub>alkyl, R<sub>2</sub> is hydrogen, R<sub>3</sub> is arylC<sub>1-4</sub>alkyl.

35

Another featured group of compounds are those compounds of formula (I) as defined herein, wherein Q<sub>2</sub> is a radical of formula (VI), and in particular those compounds of formula (I), as defined herein, wherein Q<sub>2</sub> is a radical of formula (VI), R<sub>4</sub> is C<sub>1-6</sub>alkyl, R<sub>2</sub> is hydrogen, R<sub>3</sub> is arylC<sub>1-4</sub>alkyl.

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Another featured group of compounds are those compounds of formula (I) as defined herein, wherein  $Q_2$  is a radical of formula (VII), and in particular those compounds of formula (I), as defined herein, wherein  $Q_2$  is a radical of formula (VII),  $R_4$  is  $C_{1-6}$ alkyl,  $R_2$  is hydrogen,  $R_3$  is aryl $C_{1-4}$ alkyl.

5

Another featured group of compounds are those compounds of formula (I), wherein  $Q_2$  is a radical of formula (III), and wherein A is  $-C(=O)-$  or  $C_{1-6}$ alkanediyl,  $R_5$  is hydrogen or  $C_{1-6}$ alkyl; or taken together with  $-A-R_6$  and with the nitrogen atom to which it is attached forms a Het<sup>1</sup>;  $R_6$  is  $C_{1-6}$ alkyloxy, Het<sup>1</sup>, Het<sup>2</sup>, aryl or amino; and in case -A- is other than  $C_{1-6}$ alkanediyl then  $R_6$  may also be  $C_{1-6}$ alkyl, Het<sup>1</sup> $C_{1-4}$ alkyl, Het<sup>2</sup> $C_{1-4}$ alkyl, aryl $C_{1-4}$ alkyl or amino $C_{1-4}$ alkyl; wherein each of the amino groups in the definition of  $R_6$  may optionally be substituted with one or more substituents selected from  $C_{1-4}$ alkyl, aryl $C_{1-4}$ alkyl, Het<sup>1</sup> $C_{1-4}$ alkyl or Het<sup>2</sup> $C_{1-4}$ alkyl.

10

Another interesting group of compounds are those compounds of formula (I) as defined herein, wherein  $Q_2$  is a radical of formula (VII) and wherein  $R_4$  is  $C_{1-6}$ alkyl,  $R_2$  is hydrogen,  $R_3$  is aryl $C_{1-4}$ alkyl and the Haryl moiety is selected from thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, pyrazolyl, pyrazinyl, imidazolinonyl, quinolinyl, isoquinolinyl, indolyl, pyridazinyl, pyridinyl, pyrrolyl, pyranyl, pyrimidinyl, furanyl, triazolyl, tetrazolyl, benzofuranyl, benzoxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, thiophenyl, tetrahydrofurofuranyl, tetra-hydropyranofuranyl, benzothiophenyl, carbazolyl, imidazolonyl, oxazolonyl, indoliziny, triazinyl or quinoxaliny, and (i) which is optionally substituted on one or more carbon atoms by halogen, optionally mono- or disubstituted amino, nitro, cyano,  $C_{3-7}$ cycloalkyl, optionally mono- or disubstituted aminocarbonyl,  $-(R_{7a})_n-M-R_{7b}$ , Het<sup>1</sup> or Het<sup>2</sup>; wherein the optional substituents on any amino function are independently selected from  $R_5$  and  $-A-R_6$ .

25

Accordingly, the present invention relates particularly to the use as defined herein of the sulfonamide selected from the following group:

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{3-[(2-Acetylamino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester;  
 [1-Benzyl-2-hydroxy-3-({2-[(6-hydroxy-pyridine-3-carbonyl)-amino]-benzooxazole-6-sulfonyl}-isobutyl-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester;  
 [1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(pyridine-3-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester;  
 {1-Benzyl-2-hydroxy-3-[isobutyl-(2-pyrrolidin-1-yl-benzooxazole-6-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester;

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- [1-Benzyl-2-hydroxy-3-(isobutyl-{2-[2-(4-methyl-piperazin-1-yl)-acetyl-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester;
- [1-Benzyl-3-({2-[(furan-3-carbonyl)-methyl-amino]-benzooxazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid thiazol-5-ylmethyl ester;
- 5 [1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(1-methyl-pyrrolidine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester;
- {1-Benzyl-3-[(3-benzyl-3H-benzoimidazole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester;
- {3-[(2-Amino-benzothiazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester;
- 10 (1-Benzyl-3-{[2-(2-dimethylamino-ethylamino)-benzothiazole-6-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid thiazol-5-ylmethyl ester;
- (1-Benzyl-2-hydroxy-3-{isobutyl-[2-(2-pyrrolidin-1-yl-ethylamino)-benzothiazole-6-sulfonyl]-amino}-propyl)-carbamic acid thiazol-5-ylmethyl ester;
- 15 (1-Benzyl-2-hydroxy-3-{isobutyl-[2-(2-pyrrolidin-1-yl-ethylamino)-benzothiazole-6-sulfonyl]-amino}-propyl)-carbamic acid thiazol-5-ylmethyl ester;
- (1-Benzyl-2-hydroxy-3-{isobutyl-[2-(2-piperazin-1-yl-ethylamino)-benzothiazole-6-sulfonyl]-amino}-propyl)-carbamic acid thiazol-5-ylmethyl ester;
- {3-[(2-Amino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester;
- 20 [1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(5-oxo-pyrrolidine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-yl methyl ester;
- [1-Benzyl-3-({2-[(furan-3-carbonyl)-amino]-benzooxazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid thiazol-5-ylmethyl ester;
- 25 [1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(pyridine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester;
- {3-[(2-Amino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid 2-chloro-thiazol-5-ylmethyl ester;
- (1-Benzyl-3-{[2-(2-dimethylamino-acetyl-amino)-benzooxazole-6-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid thiazol-5-ylmethyl ester;
- 30 {1-Benzyl-2-hydroxy-3-[isobutyl-(2-piperazin-1-yl-benzooxazole-6-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester;
- {1-Benzyl-2-hydroxy-3-[isobutyl-(2-piperidin-1-yl-benzooxazole-6-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester;
- 35 [1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(pyridine-4-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester;
- {1-Benzyl-2-hydroxy-3-[isobutyl-(3-isobutyl-3H-benzoimidazole-5-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester;

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[1-Benzyl-2-hydroxy-3-(isobutyl)-{4-[2-(pyridin-4-ylamino)-thiazol-4-yl]-benzene-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester;  
{3-[(2-Amino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester;

5 an *N*-oxide, a salt or stereoisomeric form thereof.

Interestingly, the compounds of the present invention may comprise chemically reactive moieties or groups capable of forming covalent bonds to localized sites such that said compound have increased tissue retention and half-lives. The term  
10 "chemically reactive group" as used herein refers to chemical groups capable of forming a covalent bond. Reactive groups will generally be stable in an aqueous environment and will usually be carboxy, phosphoryl, or convenient acyl group, either as an ester or a mixed anhydride, or an imidate, or a maleimide thereby capable of forming a covalent bond with functionalities such as an amino group, a hydroxy or a  
15 thiol at the target site on for example blood components.

Upon administration to an individual in need thereof, said compound is capable of forming covalent bonds to localized sites, with blood component for example, such that said compound according to the invention has increased tissue retention and half-lives.  
20 Usually, the covalent bond that is formed should be able to be maintained during the lifetime of the blood component, unless it is intended to be a release site. A major advantage of said new compound is the small amount of compound necessary to provide an effective effect. The reasons for this advantage are explained by the targeting of the delivery, the high yield of reaction between the reactive entity Y and  
25 reactive functionality and the irreversible nature of the bond formed after reaction. Furthermore, once bound to the membrane or tissue said compound according to the invention is not susceptible to liver metabolism, kidney filtration and excretion, and may even be protected from protease (inclusive of endopeptidase) activity which usually leads to loss of activity and accelerated elimination.

30 "Blood components" as used herein refers to either fixed or mobile blood components. Fixed blood components are non-mobile blood components and include tissues, membrane receptors, interstitial proteins, fibrin proteins, collagens, platelets, endothelial cells, epithelial cells and their associated membrane and membranous  
35 receptors, somatic body cells, skeletal and smooth muscle cells, neuronal components, osteocytes and osteoclasts and all body tissues especially those associated with the circulatory and lymphatic systems. Mobile blood components are blood components that do not have a fixed situs for any extended period of time, generally not exceeding



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5, more usually one minute. These blood components are not membrane-associated and are present in the blood for extended periods of time and are present in a minimum concentration of at least 0.1 µg/ml. Mobile blood components include serum albumin, transferrin, ferritin and immunoglobulins such as IgM and IgG. The half-life of mobile blood components is at least about 12 hours.

The compounds of formula (I) can generally be prepared using procedures analogous to those procedures described in WO 95/06030, WO 96/22287, WO 96/28418, WO 96/28463, WO 96/28464, WO 96/28465 or WO 97/18205.

Particular reaction procedures to make the present compounds are specifically described in WO 02/083657, WO 02/092595, WO 02/081478, WO 03/53435, PCT/EP03/50057, PCT/EP03/50173 or PCT/EP03/50359, which are incorporated herein specifically by reference. In these preparations, the reaction products may be isolated from the medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

It will be appreciated that the intermediates, wherein -A-R<sub>6</sub> is hydrogen, may also have pharmacological properties, similar to those pharmacological properties of the compounds of formula (I). Using methods known to the person skilled in the art, such as for instance described below, he will be able to test the efficacy and efficiency of these intermediates as well as the compounds described herein, without undue burden or the application of inventive skill.

The present compounds can thus be used in animals, preferably in mammals, and in particular in humans as pharmaceuticals per se, in mixtures with one another or in the form of pharmaceutical preparations.

Furthermore, the present invention relates to pharmaceutical preparations which as active constituents contain an effective dose of at least one of the compounds of formula (I) in addition to customary pharmaceutically innocuous excipients and auxiliaries. The pharmaceutical preparations normally contain 0.1 to 90% by weight of a compound of formula (I). The pharmaceutical preparations can be prepared in a manner known per se to one of skill in the art. For this purpose, at least one of a compound of formula (I), together with one or more solid or liquid pharmaceutical excipients and/or auxiliaries and, if desired, in combination with other pharmaceutical active compounds, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human medicine or veterinary medicine.

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Pharmaceuticals which contain a compound according to the invention can be administered orally, parenterally, e.g., intravenously, rectally, by inhalation, or topically, the preferred administration being dependent on the individual case, e.g., the particular course of the disorder to be treated. Oral administration is preferred.

The person skilled in the art is familiar on the basis of his expert knowledge with the auxiliaries which are suitable for the desired pharmaceutical formulation. Beside solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound carriers, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, agents for achieving a depot effect, buffer substances or colorants are also useful.

Due to their favorable antiviral properties, as will be apparent from the examples, the compounds of the present invention are useful in the treatment of individuals infected by HCV and for the prophylaxis of these individuals. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with flaviviruses. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HCV and other pathogenic flaviviruses, such as Yellow fever, Dengue fever (types 1-4), St. Louis encephalitis, Japanese encephalitis, Murray valley encephalitis, West Nile virus and Kunjin virus. The conditions associated with HCV include progressive liver fibrosis, inflammation and necrosis leading to cirrhosis, end-stage liver disease, and HCC; and for the other pathogenic flaviviruses the conditions include yellow fever, dengue fever, haemorrhagic fever and encephalitis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against the above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to HCV-infected subjects of an amount effective to combat the conditions associated with HCV and other pathogenic flaviviruses. Consequently, the compounds of the present invention can be used in the manufacture of a medicament useful for treating conditions associated with HCV and other pathogenic flaviviruses, in particular medicaments useful for treating patients co-infected with HCV and HIV virus.

In an embodiment, the invention relates to the use of a compound of formula (I) or any subgroup thereof as defined herein in the manufacture of a medicament for treating or combating infection or disease associated with HCV infection in a mammal. The invention also relates to a method of treating a flaviviral infection, or a disease

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associated with flavivirus infection comprising administering to a mammal in need thereof an effective amount of a compound of formula (I) or a subgroup thereof as defined herein.

- 5 In another embodiment, the present invention relates to the use of formula (I) or any subgroup thereof as defined herein for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with flaviviruses, in particular HCV.

- 10 In another embodiment, the present invention relates to the use of formula (I) or any subgroup thereof as defined herein for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with flaviviruses, wherein said HCV is inhibited in its replication.

- Also, the combination of previously known anti-HCV compound, such as, for instance, 15 interferon- $\alpha$  (IFN- $\alpha$ ), pegylated interferon- $\alpha$  and/or ribavirin, and a compound of the present invention can be used as a medicine in a combination therapy. The term "combination therapy" relates to a product containing mandatory (a) a compound of the present invention, and (b) optionally another anti-HCV compound, and/or possibly (c) an anti-HIV compound, as a combined preparation for simultaneous, separate or 20 sequential use in treatment of HCV infections, in particular, in the treatment of infections with HCV type 1, and possibly coinfecting with HIV. Thus, to combat or treat HCV infections, or the infection and disease associated with HCV infections, such as liver fibrosis, inflammation, necrosis leading to cirrhosis, end-stage liver disease and HCC, the compounds of this invention may be co-administered in combination with for 25 instance, interferon- $\alpha$  (IFN- $\alpha$ ), pegylated interferon- $\alpha$  and/or ribavirin, as well as therapeutics based on antibodies targeted against HCV epitopes, small interfering RNA (siRNA), ribozymes, DNazymes, antisense RNA, small molecule antagonists of for instance NS3 protease, NS3 helicase and NS5B polymerase.

- 30 Accordingly, the present invention relates to the use of a compound of formula (I) or any subgroup thereof as defined above for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV viruses, wherein said medicament is used in a combination therapy, said combination therapy preferably comprising a compound of formula (I) and (pegylated) IFN- $\alpha$  and/or ribavirin, and 35 possibly an anti-HIV compound.

In addition to the presently found HCV antiviral activity, their known inhibitory activity against the HIV protease enzyme renders the compounds of the present

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invention useful in the treatment of individuals co-infected with HCV and HIV and for the prophylaxis of these individuals.

Therefore, HCV infected patients also suffering from conditions associated with HIV or even other pathogenic retroviruses, such as AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic CNS diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis, can conveniently be treated with the present compounds.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to patients co-infected with HIV and HCV of an amount effective to combat the conditions associated with HCV and HIV. Consequently, the compounds of the present invention can be used in the manufacture of a medicament useful for treating conditions associated with the co-infection of HCV and HIV, including multi-drug resistant HIV virus.

In another embodiment, the present invention relates to the use of formula (I) or any subgroup thereof in the manufacture of a medicament useful for inhibiting HCV activity and HIV activity, and in particular inhibiting a protease of a multi-drug resistant HIV-1 retrovirus, in a mammal infected with both HCV and HIV.

For an oral administration form, compounds of the present invention are mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms.

For subcutaneous or intravenous administration, the active compounds, if desired with the substances customary therefor such as solubilizers, emulsifiers or further auxiliaries, are brought into solution, suspension, or emulsion. The compounds of formula (I) can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example,

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water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned.

- 5 Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of formula (I) or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as
- 10 surfactants, emulsifiers and stabilizers as well as a propellant. Such a preparation customarily contains the active compound in a concentration from approximately 0.1 to 50%, in particular from approximately 0.3 to 3% by weight.

- Another aspect of the present invention concerns a kit or container comprising a
- 15 compound of formula (I) in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HCV growth, and possibly also to inhibit HIV growth and/or HIV protease activity. This aspect of the invention may find its use in pharmaceutical research programs.
- 20 The compounds of the present invention can be used in high-throughput target-analyte assays such as those for measuring the efficacy of said compound in HCV or combined HCV/HIV treatment.

- The dose of the present compounds or of the physiologically tolerable salt(s) thereof to
- 25 be administered depends on the individual case and, as customary, is to be adapted to the conditions of the individual case for an optimum effect. Thus it depends, of course, on the frequency of administration and on the potency and duration of action of the compounds employed in each case for therapy or prophylaxis, but also on the nature and severity of the infection and symptoms, and on the sex, age, weight and individual
- 30 responsiveness of the human or animal to be treated and on whether the therapy is acute or prophylactic. Customarily, the daily dose of a compound of formula (I) in the case of administration to a patient approximately 75 kg in weight is 1 mg to 1.5g, preferably 10 mg to 1 g. The dose can be administered in the form of an individual dose, or divided into several, e.g. two, three, or four, individual doses.

- 35 Accordingly, another aspect of the present invention concerns a kit or container comprising a compound of formula (I) in an amount effective to combat, treat or ameliorate the conditions associated with HCV infection and/or HCV/HIV coinfection in a mammal.

It will be appreciated by the person skilled in the art that the compounds of formula (I) may be tested in a cellular HCV replicon system based on Lohmann et al. (1999) Science 285:110-113, with the further modifications described by Krieger et al. (2001) Journal of Virology 75: 4614-4624 (incorporated herein by reference), which is further exemplified in the examples section. This model, while not a complete infection model for HCV, is widely accepted as the most robust and efficient model of autonomous HCV RNA replication currently available. Compounds exhibiting anti-HCV activity in this cellular model are considered as candidates for further development in the treatment of HCV infections in mammals. It will be appreciated that it is important to distinguish between compounds that specifically interfere with HCV functions from those that exert cytotoxic or cytostatic effects in the HCV replicon model, and as a consequence cause a decrease in HCV RNA or linked reporter enzyme concentration. Assays are known in the field for the evaluation of cellular cytotoxicity based for example on the activity of mitochondrial enzymes using fluorogenic redox dyes such as resazurin. Furthermore, cellular counterscreens exist for the evaluation of non-selective inhibition of linked reporter gene activity, such as firefly luciferase. Appropriate cell types can be equipped by stable transfection with a luciferase reporter gene whose expression is dependent on a constitutively active gene promoter, and such cells can be used as a counterscreen to eliminate non-selective inhibitors.

All patents, patent applications and articles referred to before or below are incorporated herein by reference.

## Examples section

### *Example 1: Activity of compounds of formula (I) in HCV replicon assays*

#### **Stable replicon cell reporter assays:**

The compounds of the present invention were examined for activity in the inhibition of HCV RNA replication in a cellular assay. The assay demonstrated that these compounds exhibited activity against HCV replicons functional in a cell culture. The cellular assay was based on a bicistronic expression construct, as described by Lohmann et al. (1999) Science vol. 285 pp. 110-113 with modifications described by Krieger et al. (2001) Journal of Virology 75: 4614-4624, in a multi-target screening strategy. In essence, the method is as follows.

The assay utilized the stably transfected cell line Huh-7 luc/neo (hereafter referred to as Huh-Luc; kindly provided by Dr Ralf Bartenschlager, Replikon GmbH, Germany). This cell line harbors an RNA encoding a bicistronic expression construct comprising the wild type NS3-NS5B regions of HCV type 1b translated from an Internal Ribosome

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Entry Site (IRES) from encephalomyocarditis virus (EMCV), preceded by a reporter portion (FfL-luciferase), and a selectable marker portion (neo<sup>R</sup>, neomycine phosphotransferase). The construct was bordered by 5' and 3' NTRs (non-translated regions) from HCV type 1b. Continued culture of the replicon cells in the presence of  
 5 G418 (neo<sup>R</sup>) is dependent on the replication of the HCV RNA. The stably transfected replicon cells that express HCV RNA, which replicates autonomously and to high levels, encoding *inter alia* luciferase, were used for screening the antiviral compounds.

#### Cellular Assay Experimental Method:

- 10 The replicon cells were plated in 384 well plates in the presence of the test and control compounds which were added in various concentrations. Following an incubation of three days, HCV replication was measured by assaying luciferase activity (using standard luciferase assay substrates and reagents and a Perkin Elmer ViewLux<sup>™</sup> ultraHTS microplate imager). Replicon cells in the control cultures have high luciferase  
 15 expression in the absence of any inhibitor. The inhibitory activity of the compound on luciferase activity was monitored on the Huh-Luc cells, enabling a dose-response curve for each test compound. EC50 values were then calculated, which value represents the amount of the compound required to decrease by 50% the level of detected luciferase activity, or more specifically, the ability of the genetically linked HCV replicon RNA  
 20 to replicate (Table 1).

In table 1, column 1 provides an identification number, column 2 displays the results as EC50 on the above described Huh7-Luc assay wherein :

- ++++ means an EC50 less than 2  $\mu$ M  
 25 +++ means an EC50 between 2 and 10  $\mu$ M  
 ++ means an EC50 between 10 and 32  $\mu$ M  
 + means an EC50 greater than 32  $\mu$ M.

Column 5 provides the chemical structure of the compounds tested.

Compound	EC50 value	Compound Name
1	+++	{3-[(2-Acetylamino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester
2	++	(6-{[2-Hydroxy-4-phenyl-3-(thiazol-5-ylmethoxycarbonyl-amino)-butyl]-isobutyl-sulfamoyl}-benzooxazol-2-yl)-carbamic acid ethyl ester
3	++++	[1-Benzyl-2-hydroxy-3-( {2-[(6-hydroxy-pyridine-3-carbonyl)-amino]-benzooxazole-6-sulfonyl}-isobutyl-amino)-propyl]-

Compound	EC50 value	Compound Name
4	+++	carbamic acid thiazol-5-ylmethyl ester [1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(pyridine-3-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
5	+++	{1-Benzyl-2-hydroxy-3-[isobutyl-(2-pyrrolidin-1-yl-benzooxazole-6-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester
6	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[methyl-(2-pyrrolidin-1-yl-ethyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
7	+++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[2-(4-methyl-piperazin-1-yl)-acetylamino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
8	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[methyl-(5-oxo-pyrrolidine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
9	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[methyl-(pyridine-4-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
10	+++	[1-Benzyl-3-({2-[(furan-3-carbonyl)-methyl-amino]-benzooxazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid thiazol-5-ylmethyl ester
11	+++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(1-methyl-pyrrolidine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
12	+++	{1-Benzyl-3-[(3-benzyl-3H-benzimidazole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester
13	+++	{3-[(2-Amino-benzothiazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester
14	+++	{1-Benzyl-3-{{2-(2-dimethylamino-ethylamino)-benzothiazole-6-sulfonyl}-isobutyl-amino}-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester
15	+++	{1-Benzyl-2-hydroxy-3-{isobutyl-[2-(2-pyrrolidin-1-yl-ethyl-amino)-benzothiazole-6-sulfonyl]-amino}-propyl}-carbamic acid thiazol-5-ylmethyl ester



Compound	EC50 value	Compound Name
16	+++	(1-Benzyl-2-hydroxy-3-{isobutyl-[2-(2-pyrrolidin-1-yl-ethylamino)-benzothiazole-6-sulfonyl]-amino}-propyl)-carbamic acid thiazol-5-ylmethyl ester trifluoroacetate salt
17	++	(1-Benzyl-3-{{2-(3-dimethylamino-propylamino)-benzothiazole-6-sulfonyl}-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid thiazol-5-ylmethyl ester
18	+++	(1-Benzyl-2-hydroxy-3-{isobutyl-[2-(2-piperazin-1-yl-ethyl-amino)-benzothiazole-6-sulfonyl]-amino}-propyl)-carbamic acid thiazol-5-ylmethyl ester
19	+++	{3-[(2-Amino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester
20	++	{3-[(3H-Benzoimidazole-5-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester
21	++	(3-{[2-(Acetyl-methyl-amino)-benzothiazole-6-sulfonyl]-isobutyl-amino}-1-benzyl-2-hydroxy-propyl)-carbamic acid thiazol-5-ylmethyl ester
22	+	{3-[(2-Amino-benzooxazole-6-sulfonyl)-pyridin-2-ylmethyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester trifluoroacetate salt
23	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(5-oxo-pyrrolidine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-yl methyl ester
24	+++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(5-oxo-pyrrolidine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-yl methyl ester
25	++++	[1-Benzyl-3-({2-[(furan-3-carbonyl)-amino]-benzooxazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid thiazol-5-ylmethyl ester
26	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(1-methyl-piperidine-4-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
27	+++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(pyridine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
28	+++	{3-[(2-Amino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-

Compound	EC50 value	Compound Name
		benzyl-2-hydroxy-propyl}-carbamic acid 2-chloro-thiazol-5-ylmethyl ester
29	+++	(1-Benzyl-3-{{2-(2-dimethylamino-acetyl-amino)-benzo-oxazole-6-sulfonyl}-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid thiazol-5-ylmethyl ester
30	+++	{1-Benzyl-2-hydroxy-3-[isobutyl-(2-piperazin-1-yl-benzo-oxazole-6-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester
31	+++	{1-Benzyl-2-hydroxy-3-[isobutyl-(2-piperidin-1-yl-benzo-oxazole-6-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester
32	++	{1-Benzyl-2-hydroxy-3-[isobutyl-(2-{2-[methyl-(2-pyrrolidin-1-yl-ethyl)-amino]-acetyl-amino}-benzooxazole-6-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester
33	++	{1-Benzyl-3-[(2-dimethylamino-benzooxazole-6-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester
34	++	{3-[(2-Amino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid oxazol-5-ylmethyl ester
35	++++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[(pyridine-4-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
36	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[methyl-(pyridine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
37	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[methyl-(1-methyl-piperidine-3-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
38	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[methyl-(1-methyl-piperidine-4-carbonyl)-amino]-benzooxazole-6-sulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
39	++	[1-Benzyl-3-({2-[(2-chloro-pyridine-4-carbonyl)-methyl-amino]-benzooxazole-6-sulfonyl}-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid thiazol-5-ylmethyl ester
40	++	[1-Benzyl-2-hydroxy-3-(isobutyl-{2-[methyl-(1-methyl-pyrrolidine-2-carbonyl)-amino]-benzooxazole-6-sulfonyl}-

Compound	EC50 value	Compound Name
41	++	amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester trifluoroacetate salt {1-Benzyl-2-hydroxy-3-[isobutyl-(3-phenethyl-3H-benzoimidazole-5-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester
42	+++	{1-Benzyl-2-hydroxy-3-[isobutyl-(3-isobutyl-3H-benzoimidazole-5-sulfonyl)-amino]-propyl}-carbamic acid thiazol-5-ylmethyl ester
43	++++	[1-Benzyl-2-hydroxy-3-(isobutyl-{4-[2-(pyridin-4-ylamino)-thiazol-4-yl]-benzenesulfonyl}-amino)-propyl]-carbamic acid thiazol-5-ylmethyl ester
44	++	(1-Benzyl-2-hydroxy-3-{isobutyl-[4-(2-methyl-oxazol-4-yl)-benzenesulfonyl]-amino}-propyl)-carbamic acid thiazol-5-ylmethyl ester
45	+++	{3-[(2-Amino-benzooxazole-6-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid thiazol-5-ylmethyl ester

**Example 2: Dose preparations of the compounds of formula (I)**

**Formulation**

Active ingredient, *in casu* a compound of formula (I), is dissolved in organic solvent such as ethanol, methanol or methylene chloride, preferably, a mixture of ethanol and methylene chloride. Polymers such as polyvinylpyrrolidone copolymer with vinyl acetate (PVP-VA) or hydroxypropylmethylcellulose (HPMC), typically 5 mPa.s, are dissolved in organic solvents such as ethanol, methanol methylene chloride. Suitably the polymer is dissolved in ethanol. The polymer and compound solutions are mixed and subsequently spray dried. The ratio of compound/polymer is selected from 1/1 to 1/6. Intermediate ranges are 1/1.5 and 1/3. A suitable ratio is 1/6. The spray-dried powder, a solid dispersion, is subsequently filled in capsules for administration. The drug load in one capsule ranges between 50 and 100 mg depending on the capsule size used.

**Film-coated Tablets**

**Preparation of Tablet Core**

A mixture of 100 g of active ingredient, *in casu* a compound of formula (I), 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The

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wet powder mixture is sieved, dried and sieved again. Then there is added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

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*Coating*

To a solution of 10 g methylcellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethylcellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated color suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

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